REMARKS

Claims 45-60 are pending in this application. Claims 45-56 are rejected under 35 U.S.C. § 102(b) for anticipation by Constantz et al. (U.S. Patent No. 5,782,971; hereinafter "Constantz"), and under 35 U.S.C. § 102(e) for anticipation by Poser et al. (U.S. Patent No. 5,968,253; hereinafter "Poser"). Claims 45-58 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld") in view of Amerongen et al. (U.S. Patent No. 5,443,832; hereinafter "Amerongen") and Constantz, and claims 45-60 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in view of Amerongen, Constantz, Gupta et al. (Vaccine Design, Chapter 8, pp. 229-248, 1995; hereinafter "Gupta"), and Kossovsky et al. (U.S. Patent No. 5,462,751; hereinafter "Kossovsky"). Finally, claims 45-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,214,368 (hereinafter "the '368 patent"), claims 1-7 of U.S. Patent No. 6,117,456 (hereinafter "the '456 patent"), and claims 1-12 of U.S. Patent No. 5,683,461 (hereinafter "the '461 patent"). By this reply, Applicants amend the specification, amend claims 45-54 and 56-60, cancel claim 55, add new claims 61-72, and address each of the Examiner's rejections below.

Support for the Amendment

Support for the amendment to claims 45, 59, and 60 is found in the specification on, e.g., page 10, lines 4-7, and page 11, lines 20-22. Support for the amendment to claim 46 and for new claim 61 is found in the specification on, e.g., page 41, lines 17-21. Support for the amendment to claims 47-54 and 56 and for new claims 62-71 is found in prior claims 47-54 and 56. Support

for the amendment to claim 58 and for new claim 72 is found in the specification on, e.g., page 10, line 12, through page 11, line 4. No new matter is added by the amendment.

Priority

Applicants note that priority of the instant application has been determined to be September 15, 1998, and therefore, Applicants have appropriately amended the first page of the specification to delete reference to the earlier applications. Applicants reserve the right to establish an earlier priority date for this application, if necessary.

Obviousness-Type Double Patenting Rejections

The Examiner rejects claims 45-60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of the '368 patent, claims 1-7 of the '456 patent, and claims 1-12 of the '461 patent. In response to the double patenting rejection, Applicants will submit a terminal disclaimer, if necessary, once otherwise allowable subject matter has been determined.

Rejections under 35 U.S.C. § 102

Constantz

Claims 45-56 are rejected under 35 U.S.C. § 102(b) for anticipation by Constantz. The Examiner states:

> Constantz...meets all elements of the instant claims. Constantz disclose[s] injectable paste compositions comprising amorphous calcium phosphate mixtures in combination with a second calcium source such as hydroxyapatite, tetra calcium phosphate in amounts higher than 40 wt%...Thus Constantz anticipates

the limitations of the instant claims. (Office Action, p. 4.)

Applicants respectfully disagree. Applicants also note that the claims have been amended, and the differences between the claims, as amended, and Constantz are now even more readily apparent.

Independent claim 45 has been amended and is now directed to an immunological vaccine delivery composition containing a calcium phosphate and an active agent that is present in an amount sufficient to elicit a host response that protects the host against a pathogen. Constantz fails to teach or suggest a composition that delivers an active agent to a host that stimulates a protective immune response against a pathogen, as is recited in present claim 45 and claims dependent therefrom. Constantz merely discloses a flowable calcium phosphate composition capable of setting *in vivo* for use in the treatment of compromised hard tissue (see col. 2, lines 41-44).

The Examiner argues that Constantz anticipates pending claim 45, and claims dependent therefrom, because the calcium phosphate containing compositions of Constantz can be combined with various organic compounds, e.g., proteins and growth factors, which are encompassed by generic terms such as antigens, hapten, allergen, or immunogen (see p. 4 of the Office Action). Further, the Examiner states:

> a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. *In re Casey*, 152 USPQ 235 (CCPA 1967). In the instant case, Constantz meets all elements of the instant claims and [is] thus capable of performing the instant intended use and functional characteristics set forth in claims 51-53. (Office Action, p. 5.)

Because Constantz does not disclose a calcium phosphate composition containing an active agent

that is capable of eliciting a host immune response that is protective against a pathogen, Constantz does not meet all the elements of present claim 45, and claims dependent therefrom. Constantz merely discloses:

> a number of additional ingredients which provide desirable properties to the final cement...include organic polymers, e.g., proteins, including bone associated proteins which impart a number of properties, such as enhancing resorption, angiogenesis, cell entry, and proliferation, mineralization, bone formation, growth of osteoclasts and/or osteoblasts, and the like...
>
> The subject calcium phosphate cements may be used for a variety of purposes, such as any form of connective tissue replacement, including bone cement, an injected prosthetic implant, a prosthetic orthopaedic or dental implant, as a root canal filler, a prophylactic injection to augment weak osteoporotic bone, to fill voids resulting from fracture reduction, or a vehicle for drug delivery. (Col. 5, lines 57-67, and col. 6, lines 56-62.)

Constantz clearly intends the calcium phosphate composition to be used for the repair of compromised bone or for the delivery of osteogenic proteins to facilitate the repair of compromised bone. Therefore, the proteins and growth factors contained in the Constantz composition are clearly included to provide a therapeutic benefit to the host to which the composition is administered. Constantz does not teach or suggest that the calcium phosphate composition can or should be used to deliver an active agent to a host specifically to elicit a protective immune response against a pathogen. More than that even, the Constantz composition does not have the functional characteristics of, nor would it be used in the same manner as, the composition of present claim 45, as is suggested by the Examiner (see p. 5 of the Office Action), because the Constantz composition would clearly not be used to stimulate a host immune response to protect the host against a pathogen. For this reason as well, Constantz fails to anticipate present claims 45-54 and 56. Therefore, Applicants respectfully request that the rejection of

claims 45-56 under 35 U.S.C. § 102(b) for anticipation by Constantz be withdrawn.

Poser

Claims 45-56 are rejected over 35 U.S.C. § 102(e) for anticipation by Poser. The Examiner states:

> Poser meets all elements of the instant claims. Poser...discloses the use of tricalcium phosphate particles and amorphous calcium phosphate as suitable calcium phosphates. In addition, Poser discloses the use of penicillins and cephlosporins with his compositions. Such therapeutic agents are well recognized as classic haptens, allergens or immunogens. Therefore, Poser's teachings anticipate the limitations of the instant claims. (Office Action, pp. 5-6.)

Applicants respectfully disagree.

Poser merely discloses a calcium phosphate bone cement containing an antimicrobial agent (see, e.g., Abstract of Poser). An antimicrobial agent, such as an antibiotic, would clearly be administered to kill or inhibit the growth of a pathogen that had infected a host by acting on the pathogen directly. An antimicrobial agent would not be administered to a host to elicit an immune response, which would then be used to protect the host against the invading pathogen. Furthermore, an antimicrobial agent that did elicit an immune response would not be useful to the host because it would preclude subsequent administration to the host. Therefore, an antimicrobial agent would not be administered to a host for the purpose of eliciting an immune response.

In fact, Poser does not intend for the antimicrobial agent-containing bone cement to be administered for the purpose of eliciting a host immune response, stating "[t]he amount of the antimicrobial agent that is present in the cement will be sufficient to provide for a product that at least reduces the growth rate of microbial organisms in the region of the product as compared to

a control" (see col. 6, lines 31-34, of Poser). Clearly, Poser fails to teach or suggest that the antimicrobial agent-containing bone cement is provided to elicit a host immune response that then protects the host against a pathogen, or that the bone cement is an immunological vaccine delivery composition, as is recited in present claim 45, and claims dependent therefrom. Further, the Poser composition does not have the functional characteristics of, nor would it be used in the same manner as, the composition of present claim 45, because it would clearly not be used to elicit a protective immune response against a pathogen in a host that received the composition. Therefore, Poser, like Constantz, does not teach or suggest every limitation of present claims 45-54 and 56. Accordingly, Applicants respectfully request that the rejection of claims 45-56 under 35 U.S.C. § 102(e) for anticipation by Poser be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Relyveld, Amerongen, and Constantz

Claims 45-58 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in view of Amerogen and Constantz. The Examiner states:

> ...one of ordinary skill in the art at the time of invention would have modified the concentrations of Relyveld calcium phosphate adjuvant composition to contain about 40 wt % solid component by routine experimentation and further formulate a hardenable calcium phosphate formulation, per teachings of Amerongen and Constantz, because even at higher concentration of solid components, such compositions are easily administered to the site of interest to elicit their intended clinical effects. (Office Action, p. 7.)

The Examiner also states that because Relyveld and Amerongen disclose that calcium phosphate elicits an immune response at lower concentrations, it flows logically that calcium phosphate can also elicit an immune response at higher concentrations, and one of ordinary skill in the art would

have been able to ascertain such amounts by routine experimentation. Applicants respectfully disagree. First, Constantz constitutes non-analogous art not pertinent to the problem addressed by Applicants. Second, contrary to the Examiner's assertion, there is no motivation to modify Relyveld to yield the present invention based on the disclosure of Constantz or Amerongen. Third, nothing in Relyveld suggests looking beyond what is taught. Fourth, the Examiner has engaged in an impermissible hindsight reconstruction of Applicants' invention.

Constantz is Nonanalogous Art and Has Been Improperly Combined with Relyveld and Amerongen

The law is clear with regard to the scope of the prior art to be considered when resolving the question of obviousness under 35 U.S.C. § 103. Applicants are presumed to have full knowledge of all prior art within the field of the endeavor (analogous art) but, with regard to prior art outside the field of endeavor (nonanalogous art), the law only presumes knowledge from those arts reasonably pertinent to the particular problem. *In re Wood,* 599 F.2d 1032, 1036 (C.C.P.A. 1979). To determine whether the prior art falls within the field of Applicants' endeavor, the courts have held that the reference and the claimed invention must share "essentially the same function and structure." *In re Deminski*, 796 F.2d 436, 442 (Fed. Cir. 1986). In further refining the analogous art requirements set forth in *In re Wood* and *In re Deminski*, the Federal Circuit construed the "field of endeavor" analysis very narrowly, holding that the field is more narrow than a single industry; *In re Clay*, 966 F.2d 656 (Fed. Cir. 1992) (holding that a prior art reference was not within the inventor's field of endeavor merely because both related to the same industry, the petroleum industry).

If a reference is not within the inventor's field of endeavor, it may still be properly combined, for § 103 purposes, if it is reasonably pertinent to the inventor's problem. *In re Wood*, at 1036. Here again, though, the courts have construed the issue of reasonable pertinence very narrowly. The Federal Circuit held that (*In re Clay* at 659; emphasis added):

> A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem. Thus, the purposes of both the invention and the prior art are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve. If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem, and that fact supports use of that reference in an obviousness rejection. An inventor may well have been motivated to consider the reference when making his invention. If it is directed to a different purpose, the inventor would accordingly have had less motivation or occasion to consider it.

Thus, for a reference to be considered prior art for purposes of a § 103 rejection, it must be either (i) analogous art, sharing essentially the same structure and function as the claimed invention, or (ii) non-analogous art having reasonable pertinence to the inventor's problem. Constantz fails to satisfy either of these criteria because it neither shares the same structure and function as the claimed invention (i.e., a calcium phosphate composition containing an active agent that elicits a protective immune response in a host), nor does it reasonably address the problems with which the present inventors were concerned (i.e., delivery of an immunogenic active agent specifically for the purpose of stimulating an immune response against a pathogen).

Field of Invention

Applicants' invention relates to the field of vaccine compositions. The invention solves the problem of how to deliver an immunogenic active agent to a host in order to stimulate the

host's immune system to produce a protective immunological response against a pathogen. The inventive calcium phosphate paste composition, once injected, hardens *in vivo* and serves as a depot of the immunogenic active agent, which is released as the composition is resorbed by the host (Specification, p. 10, lines 4-10). Constantz, in contrast, concerns the unrelated field of bone cements for use in the repair of compromised hard tissue, and never suggests any use for this composition that is remotely related to the problem solved by Applicants. Constantz merely discloses a calcium phosphate composition that contains a therapeutic agent, not an agent that elicits an immune response that protects a host against a pathogen. Constantz is, simply, not analogous art and should be removed as the basis for a rejection under 35 U.S.C. § 103.

Problem to be Solved

The problem addressed by Applicants relates to the delivery of an immunogenic active agent that will stimulate a protective host response against a pathogen. The pertinent art, therefore, for purposes of § 103 is not art in the field of bone repair compositions, the field of Constantz, but rather the completely unrelated field of vaccine formulations. Applicants solved their problem by determining that an effective host immune response could be achieved by release of an immunogenic active agent from a hardenable, injectable calcium phosphate composition following resorption of the composition by the host. Applicants' composition can be easily administered and would not require subsequent removal from the host.

In contrast, Constantz provides bone cement compositions that contain an osteogenic component for repairing compromised hard tissue (i.e., bones; see, e.g., abstract and col. 5, line 57, through col. 6, line 10, of Constantz); a problem which is clearly unrelated to the field of

vaccine formulations. Constantz neither teaches nor suggests the delivery of active agents for stimulating a host immune response, nor does Constantz teach or suggest that the bone cement could be used for such a purpose. Constantz merely describes using the bone cement to repair bone or to deliver osteogenic proteins useful for repairing bone. Thus, there is nothing in Constantz that has anything to do with the problem addressed by Applicants. Accordingly, Constantz should not be relied upon for establishing a rejection under 35 U.S.C. § 103.

There is No Motivation to Modify Relyveld and Combine with Constantz and Amerongen

The Examiner argues that one of ordinary skill in the art would have modified Relyveld, per the teachings of Amerongen and Constantz, to yield the composition of present claim 45, and claims dependent therefrom, because "even at higher concentration of solid components, such compositions are easily administered to the site of interest to elicit their intended clinical effects (Office Action, p. 7). Applicants respectfully disagree.

Even putting aside the nonanalogous art issue with respect to Constantz, there would have been no motivation to combine Constantz, which is directed to bone cements, with Relyveld or Amerongen, which are directed to vaccine formulations. Even if these references were not directed to completely different fields, one skilled in the art would not be motivated to modify Relyveld, a reference directed to a low solids content calcium phosphate-containing vaccine composition, with Constantz, which discloses high solids content calcium phosphate bone cement.

Relyveld and Amerongen disclose calcium phosphate-based vaccine formulations that contain a solids content two orders of magnitude less than the adjuvant composition of present

claim 45, while Constantz discloses high solids content calcium phosphate cements prepared using two or more calcium sources for the treatment of injured or compromised bone tissue. Although the skilled artisan would have reason to combine Relyveld with Amerogen because both of these references are directed to calcium phosphate vaccine formulations, the skilled artisan would have no reason to further combine these references with Constantz, which is directed to calcium phosphate bone cement compositions. Furthermore, neither Relyveld nor Amerongen teach or suggest substantially increasing the solids content of the calcium phosphate composition beyond that of about 3.3 wt %, as is disclosed in Relyveld, while Constantz fails to teach or suggest the use of calcium phosphate bone cements for formulating vaccine compositions. Therefore, the skilled artisan would have no motivation to combine references related to vaccine formulations (Relyveld and Amerongen), with a reference related to bone repair (Constantz) due to their disparate teachings, much less to modify these disclosures to produce the adjuvant composition of present claims 45-54 and 56-58.

Furthermore, Amerongen teaches away from increasing the solids content of the calcium phosphate composition, stating that "[i]n preferred embodiments...the hydroxylated calcium phosphate is in the form of microparticles suitable for transport across the epithelium" (see col. 2, lines 63-66). Increasing the solids content of the composition described by Amerongen would run counter to the disclosure of Amerongen and would negate the benefit of that composition (i.e., its ability to diffuse across the cell epithelium and to provide a large surface area for antigen adsorption, see below).

Constantz, on the other hand, fails to provide any teaching or suggestion to use the disclosed bone cement as a vaccine composition, or even to use a high solids content cement

where a low solids content composition is typically preferred, such as in vaccine formulations. Thus, Applicants can find no motivation to combine Constantz, which is directed to a high solids content bone substitute material, with Relyveld and Amerongen, which describe low solids content vaccine formulations.

In addition, it is unclear to Applicants why one of ordinary skill in the art would be motivated to dramatically change the established working concentrations of a vaccine formulation having a low solids content of 0.5-3.3 wt %, as is disclosed by Relyveld and Amerongen, to greater than or equal to 40 wt %, as is recited in present claims 45-54 and 56-58, based solely on the disclosure of Constantz, when Relyveld and Amerongen clearly show efficacy of the low solids content compositions for use as adjuvants and Constantz is silent with respect to the use of calcium phosphate compositions to elicit an immune response. The Examiner argues that one skilled in the art would have modified Relyveld by routine experimentation and, based on the teachings of Amerongen and Constantz, would have been motivated to formulate a hardenable calcium phosphate vaccine formulation because even at higher concentrations such compositions are easily administered to the site of interest to elicit their intended clinical effects (see Office Action, p. 7). Furthermore, the Examiner argues that the skilled artisan would have used high solids content calcium phosphate compositions, as taught by Constantz, in a vaccine formulation, as taught by Relyveld, because this is the next logical step (Office Action, p. 7). Applicants respectfully disagree.

The M.P.E.P. § 2143.01 states

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary

skill in the art. (Emphasis added.)

In the present case, the Examiner arrives at the claimed invention by combining reference teachings where there is no explicit or implicit suggestion or motivation to do so. Accordingly, the Examiner has relied solely on the knowledge of the skilled artisan and common sense as his reasons for substantiating the combination of Relyveld, Amerongen, and Constantz to establish the obviousness rejection. This justification for rejecting claims 45-58 for obviousness is improper as M.P.E.P. § 2143.01 also states:

> [The f]act that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte levengood*, 28 uspq2d 1300 (bd. Pat. App. & inter. 1993). See also *in re kotzab,* 217 f.3d 1365, 1371, 55 uspq2d 1313, 1318 (Fed. Cir. 2000).

Furthermore, M.P.E.P. § 2143.02 states:

> It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697 ("[T]he Board cannot simply reach conclusions based on its own understanding or experience—or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings."). While the court explained that, "as an administrative tribunal the Board clearly has expertise in the subject matter over which it exercises jurisdiction," it made clear that such "expertise may provide sufficient support for conclusions [only] as to peripheral issues." *Id.* at 1385-86, 59 USPQ2d at 1697. As the court held in *Zurko*, an assessment of basic knowledge and common sense that is not based on any evidence in the record lacks substantial evidence support. *Id.* at 1385, 59 USPQ2d at 1697.

Therefore, to meet his burden, the Examiner must provide some objective reason why the skilled artisan would combine and modify the disclosure of Relyveld, Amerongen, and

Constantz to arrive at the invention of present claims 45-54 and 56-58. Simply stating that the skilled artisan "would have modified" the vaccine formulation of Relyveld based on Amerongen and Constantz, or that the present invention was the "next logical step", fails to provide an "objective reason" why the references would have been combined and modified in the first place. There is simply no teaching or suggestion in Relyveld or Amerongen to increase the solids content of the disclosed vaccine compositions, and no teaching or suggestion in Constantz to use the high solids content cement compositions in a vaccine formulation. As is discussed above, there is no connection between Constantz, which is directed to bone cements, and Relyveld and Amerongen, which are directed to vaccine formulations, but provide no motivation to increase the solids content of the disclosed formulations. The Examiner has combined these references merely because they disclose compositions that use calcium phosphate, which is an insufficient basis for combination (see *In re Clay*, *supra*). There is simply no "objective reason" disclosed in any of Relyveld, Amerongen, or Constantz to substantially modify the solids content of their respective compositions. Therefore, because the Examiner has failed to provided any reason beyond ordinary skill and common sense, which are not appropriate reasons for combining and modifying prior art references to establish an obviousness rejection (see M.P.E.P. §§ 2143.01 and 2143.02), the Examiner's basis for the obviousness rejection is untenable, and the rejection of claims 45-58 should be withdrawn.

Finally, the Examiner argues that "the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious" (citing Ex parte

Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Because the skilled artisan would have no reason to combine the teachings of Relyveld, Amerongen, and Constantz, as is discussed above, the advantage of the invention of present claims 45-54 and 56-58 would not have been apparent to the skilled artisan at the time of the invention. Therefore, for this reason as well, the present rejection of claims 45-58 for obviousness should be withdrawn.

Relyveld Does not Motivate an Artisan to Look Beyond Relyveld's Own Teachings

Relyveld discloses an aqueous gel of calcium phosphate (i.e., a low solids content vaccine formulation) for use in the preparation of adsorbed vaccines (Abstract). Relyveld indicates that

> it is highly desirable that the particles of the suspension be as fine as possible. This requirement is well met by the gel of the present invention, which exhibits a marked colloidal character. The fineness of particles in the gel of the invention is demonstrated by the fact that the velocity of settling of the gel is much slower than that of conventional calcium phosphate gel. (Col. 2, lines 2-9.)

Therefore, the advantage of the Relyveld composition is its ability to remain a fine particulate gel composition that is capable of providing a large surface area for antigen adsorption. This advantage would be perceived by the skilled artisan at the time of invention as being negated by providing the immunogenic active agent in a solid block composition. Accordingly, one skilled in the art would not be motivated to look beyond the teachings of Relyveld to produce the hardenable, injectable calcium phosphate vaccine delivery composition of present claim 45, and claims dependent therefrom. To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (see M.P.E.P. § 2143.01 above). The Examiner argues that one of ordinary skill in the art at the time

of invention would have modified Relyveld based on Constantz and Amerongen (Office Action, p. 7). As is discussed above, a person of ordinary skill would not look to the field of bone cements and hardenable solid block compositions (i.e., Constantz) to address the issue of how best to deliver an active agent for stimulating an immune response. Amerongen likewise fails to motivate the skilled artisan to look beyond its teachings to develop a hardenable, injectable calcium phosphate vaccine delivery composition, as is recited in present claim 45, and claims dependent therefrom, because the advantage of the Amerongen calcium phosphate gel composition, like that of the Relyveld composition, is premised on the perceived importance of the gels' large surface area for antigen adsorption (see, e.g., Gupta). For this reason as well, the rejection of claims 45-58 for obviousness over Relyveld in combination with Constantz and Amerongen should be withdrawn.

Hindsight Reconstruction of Applicants' Invention Using Applicants' Own Disclosure as a Guide is Impermissible

The Examiner states that "[i]n the instant case, the combined teachings of all references meet all the limitations of the instant claims. Therefore, the rejection is proper" (Office Action, p. 6). Applicants respectfully disagree.

In asserting the obviousness rejection under 35 U.S.C. § 103, the Examiner has engaged in improper hindsight reconstruction of Applicants' invention. The Federal Circuit has repeatedly cautioned against the "insidious effects of hindsight" in making obviousness determinations. *Life Technologies, Inc. v. Clontech Labs, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). More specifically, the court has stated:

> it is impermissible to first ascertain factually what [Applicants] did and then view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art. (*Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985)).

To avoid the use of hindsight, the M.P.E.P. has adopted the same view, stating that "the mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness," and that the art must provide "an objective reason to combine the teachings." M.P.E.P. § 2143.01. As is discussed above, the Examiner has failed to satisfy this standard. Further, a generally high level of skill in the art cannot be relied upon to provide such a reason. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). Thus, absent a specific motivation to combine references, a *prima facie* case of obviousness cannot be made.

In the present case, the Examiner has failed to provide any evidence of a specific motivation found in the cited references that would lead the skilled artisan to the invention of present claims 45-58. The Examiner has simply found all the limitations of the present claims in the cited references and, arguing that the skilled artisan "would have" modified the disclosure of the references to yield the present invention of claims 45-58, has concluded that these claims are obvious. As is discussed below, the Examiner is improperly relying on hindsight reconstruction to sustain the obviousness rejection.

The Motivation to Combine or Modify the Cited References is Found Solely in Applicants' Specification

As is discussed above, Relyveld and Amerongen disclose low solids content calcium phosphate vaccine compositions, while Constantz, which is nonanalogous art, as is discussed

above, discloses high solids content calcium phosphate bone cement compositions. Neither Relyveld nor Amerongen teaches or suggests increasing the solids content of the calcium phosphate vaccine compositions to obtain a composition with a solids content that is nearly two orders of magnitude higher (i.e., to 40 wt %). Constantz, which discloses high solids content cement compositions that are useful in the treatment of bone, fails to provide any teaching or suggestion that such cement compositions would find utility in applications where high solids content compositions are typically not desired or required by the prior art (e.g., in vaccine formulations). Thus, the Examiner has erroneously combined a reference directed to a bone cement, with references that call for a low solids content, aqueous suspension of calcium phosphate for use as an adjuvant. By relying solely on ordinary skill and common sense, as the Examiner has done in the present case, the Examiner fails to provide an objective reason why the references would be combined and modified, as is required (see M.P.E.P. § 2143.01, *supra*). Because Relyveld, Amerongen, and Constantz fail to provide any motivation to modify the compositions disclosed therein to yield the composition of present claims 45-54 and 56-58, this motivation must be found solely in Applicants' specification. Because the Examiner has relied on hindsight reconstruction to provide a basis for the combination of references and their modification, which is improper, the obviousness rejection of claims 45-58 should be withdrawn (*Interconnect Planning Corp. v. Feil, supra*).

Finally, the Examiner also states that nonobviousness cannot be demonstrated by attacking references individually when those references have been combined as the basis for an obviousness rejection (Office Action, p. 6; citing *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Of course, that does not mean that every sentence contained in the reply

must discuss all of the references; that would be totally impractical and counterproductive.

Applicants arguments clearly address the Examiner's basis for the combination of references. The Examiner has failed to provide any objective reason why one skilled in the art would combine and modify Relyveld, Amerongen, and Constantz. As is discussed above, these references clearly fail to teach or suggest the preparation of a calcium phosphate composition having a solids content of 40 wt %, and further, they fail to provide any motivation to modify their respective compositions to achieve a calcium phosphate composition having a solids content of 40 wt %. The Examiner cannot rely solely on ordinary skill and common sense to establish such motivation; it must be taught or suggested by the references. Therefore, Applicants have discussed each reference individually to point out the flaw in the Examiner's reasons for combining the references.

Relyveld, Amerongen, Constantz, Gupta, and Kossovsky

Claims 45-60 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in view of Amerongen and Constantz, as applied to claims 45-58, and further in view of Gupta and Kossovsky. The Examiner states that "Gupta and Kossovsky further teach that calcium phosphate products are used in vaccine formulations and [are] thus capable of eliciting an immune response. Therefore, the claims stand rejected" (Office Action, pp. 8 and 9). Applicants respectfully disagree.

As is discussed above, the skilled artisan would have no reason to combine Relyveld with Amerongen and Constantz to yield the invention of present claims 45-54 and 56-58; such motivation is only provided by Applicants' specification. Gupta and Kossovsky also fail to teach

or suggest administering a vaccine formulation in the form of a paste having a solids content of greater than or equal to 40 wt %. Therefore, these references also fail to provide the necessary suggestion or motivation to combine their disclosure with Constantz, which discloses a high solids content calcium phosphate cement composition, not a vaccine formulation. Because Gupta and Kossovsky, like Relyveld and Amerongen, fail to provide any objective reason to increase the solids content of the vaccine compositions, they also fail to provide any motivation for the skilled artisan to combine their teachings with that of Constantz to yield the invention of present claims 45-54 and 56-60. For this reason, the combination of Relyveld, Amerongen, Constantz, Gupta, and Kossovsky is improper and cannot be used to establish a rejection of claims 45-60 under 35 U.S.C. § 103, nor should these references be used to establish a rejection of new claims 61-72. Accordingly, Applicants respectfully request that the rejection of claims 45-60 under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including June 15, 2004, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: June 15, 2004

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